Estimating Cancer Risks from Low Doses of Ionizing Radiation

Charles E. Land

Summary. Disagreements about the somatic risks from low doses of ionizing radiation stem from two difficulties fundamental to the logic of inference from observational data. First, precise direct estimation of small risks requires impracticably large samples. Second, precise estimates of low-dose risks based largely on high-dose data, for which the sample size requirements are more easily satisfied, must depend heavily on assumptions about the shape of the dose-response curve, even when only a few of the parameters of the theoretical form of the curve are unknown.

We probably know more about the carcinogenic effects of ionizing radiation than about those of any other environmental agent. There is a wealth of epidemiologic information, some with good dosimetry and some for which we have only an estimate of average dose to all persons exposed. There is a vast experimental literature, the mechanisms of physical damage to cellular material that may eventually result in cancer appear to be reasonably well understood, and there is wide agreement on a general mathematical form for the relation between radiation dose and cancer incidence (*1*-*3*).

Perhaps for that reason, and certainly because of the undeniable benefits associated with the use of radiologic and nuclear technology, we have been asking difficult questions about the dose-effect relations for radiation-induced cancer. The answers to these questions are often unclear; in particular, reasonable men have disagreed by as much as a factor of 100 or more in their assessment of the risk from exposures to a single rad of sparsely ionizing radiation, like x-ray or gamma rays (*4*).

We have good information, and there is relatively little disagreement, about cancer risks from exposures to hundreds of rads, but except for fetal exposure we have very little direct information about the possible effects on human beings of a single rad. Most of the disagreement about low-dose risk estimates centers on attempts to interpret low-dose data, or to extrapolate to the low-dose range the relatively good information about risks from high-dose exposures. These attempts are severely handicapped by statistical difficulties that can be best understood by considering a number of examples.

Sample Size Requirements

We have little direct information about the carcinogenic effects of low doses of sparsely ionizing radiation because the sample sizes necessary to obtain such information are impracticably large. The sample size for adequate power to test for an exposure effect, and for adequate precision in estimating that effect, depends on the underlying cancer risk due to exposure. A smaller radiation dose corresponds to a smaller excess risk, and as the excess risk decreases, a progressively larger sample is required in order to detect it. For example, if the excess risk is proportional to dose, and if a sample of 1000 persons is necessary to determine the effect of a 100-rad exposure, a sample of 100,000 may be needed for a 10-rad exposure and about 10 million for 1 rad.

This relation, which has been discussed by Pochin (*5*) in the context of estimating the increased health risk to populations in areas of unusually high background radiation, follows from the fact that excess risk must be estimated as the difference between the estimated risk in a population exposed to higher than usual radiation levels and that in a population exposed to usual levels. As excess risk decreases, sample size must increase approximately as its inverse square to maintain statistical precision and power, a relation that holds roughly so long as the excess risk remains below about one-fourth the normal risk.

Another problem, which is tangential to the main theme of this article and which will not be discussed further, is that subtle sources of bias, such as small, consistent errors in the ascertainment or reporting of exposure or disease, and confounding by other risk factors, may be comparable in effect to exposure. Increasing the sample size cannot compensate for such bias, and may in fact add to the difficulties of maintaining strict control over the observations. On the other hand, when the excess risk due to radiation is high, such biases often can be safely ignored.

Statistical Precision and Power

The statistical precision of an estimate is indicated by the ratio of its expected value, the true excess risk δ, to its standard deviation σ. If δ/σ is as large as 10, the estimate is unlikely to be more than a few percentage points different from δ. Conversely, if the ratio is as small as 1, deviations of 100 percent or more from the true value are the rule.

Statistical power, the probability of getting a statistically significant result, also varies with δ/σ. Power is the chance of correctly rejecting a false null hypothesis, in this instance the hypothesis of no radiation effect. The usual hypothesis test rejects when the estimate is greater than some multiple of either σ or some estimate of σ. Power is high if δ/σ is large; if the ratio is small power is low and it is unlikely that the null hypothesis will be rejected.

The lower limit for power, given $\delta > 0$, is the hypothetical probability of rejection given $\delta = 0$, an arbitrary small number (for example, .05) which is one of the determinants of the rule for rejecting the null hypothesis. Because failure to reject the null hypothesis is likely both under the null hypothesis and for positive values of δ for which power is low, its occurrence does not constitute strong evidence for the null hypothesis. This is particularly true if power is low for effect levels expected according to other data. Thus the results of a study based on low doses of radiation are likely to be inconclusive; in effect, the study is likely to be regarded as a wasted effort.

The author is a health statistician with the Environmental Epidemiology Branch of the National Cancer Institute, Bethesda, Maryland 20205.

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"Negative" and "Positive" Results

A negative estimate is not unlikely if power is low, and such a result can be interpreted, however improperly, as evidence that there is no excess risk associated with exposure to low-dose radiation, or even that such exposure may be beneficial. A more serious problem, because it is less well understood, follows from the fact that even when power is low, the chances of rejecting the null hypothesis are not negligible. If the lower limit for power is .05, and if the test rejects the null hypothesis whenever the estimate is greater than 1.645σ, for example, the probability of rejection is at least .05, whatever the value of δ/σ. But if $1.645\ \sigma$ is larger than δ, the estimate must also be larger than δ in order for the null hypothesis to be rejected. If all estimates received equal attention and if studies of large populations exposed to low doses of radiation were easy to do, this would present no problems, at least in the long run. Unfortunately, estimates of an effect are not very interesting if unaccompanied by evidence that the effect in fact exists, and it is a commonplace among scientists that "positive" studies—those in which the null hypothesis of no treatment effect is rejected—are more likely to be reported and published than "negative" studies, which tend to be inconclusive.

Large studies involve great effort and expense and for that reason are unlikely to go unreported; for the same reason, many possible effects tend to be investigated on the same body of data, and it is the statistically significant estimates that receive the most attention. A case in point is the recently reported investigation by Mancuso *et al.* of cancer mortality and radiation dose among workers at the Hanford Plutonium Works (*6*). These data have also been analyzed by several different investigators (*7–10*), and while the evidence for some effects, for example, lung cancer (*11*), is in dispute on methodological grounds, including adjustment for bias, all analyses obtain statistically significant estimates for two cancers, multiple myeloma and cancer of the pancreas. For these cancers, which are not among the more prominent effects seen in populations exposed to higher radiation levels, the estimates from the Hanford data are very high indeed, much higher than those obtained from other data (*12*). On the other hand, no excess is seen for leukemia, usually the most prominent of radiation-associated cancers. Understandably, public attention appears to have focused on the very high risk estimates obtained for pancreatic cancer and multiple myeloma and not on the absence of a leukemia effect; yet both findings are at variance with a considerable body of other data. With average doses of about 1 rem among exposed workers, and only 2200 deaths from all causes, the study is certainly one of low power according to current estimates of cancer risk from ionizing radiation, however, and the pattern of results is consistent with what might be expected from a study of low power.

Example: Breast Cancer

The following hypothetical example illustrates some of these points. Suppose that half of a sample of N women have received a single mammographic examination resulting in an average tissue dose of 1 rad to both breasts. Suppose the exposed and nonexposed women are otherwise comparable, that all were 35 years old at the time of exposure, and that there are 20 years of follow-up information with respect to breast cancer for each woman. The first 10 years are ignored as being too soon for any breast cancers induced by the mammographic examination to appear. About 1910 breast cancers per million women per year would normally be expected during the second 10 years (*13*) plus, in the exposed, about six additional cancers per million per year (*4, 14*).

The numbers of breast cancers observed in the exposed and nonexposed women, respectively, are approximately distributed as independent Poisson variates with respective means (and variances) equal to $^1/_2 \times N \times 10$ times 1916×10^{-6} for the exposed and times 1910×10^{-6} for the nonexposed. The estimate $\hat{\delta}$, obtained as the difference between the numbers of breast cancers divided by the numbers of years of observation for risk, or $^1/_2 \times N \times 10$ for each group, has mean $\delta = 6 \times 10^{-6}$ and standard deviation $\sigma = [(1916 + 1910) \times 10^{-6}/(^1/_2 \times N \times 10)]^{1/2} = .02766/N^{1/2}$. For simplicity σ is assumed known, contrary to the usual situation, but because we are considering only very large values of N that is not misleading; the usual estimate of σ itself has standard deviation proportional to N^{-1}. For N greater than 10,000, $\hat{\delta}$ has approximately a normal distribution. Finally, we ignore the small difference between the above value for σ and that corresponding to the null hypothesis of no excess risk, $\sigma = .02764/N^{1/2}$. Accordingly, the calculations given below are based on normal approximations to the distributions of the estimate $\hat{\delta}$, with mean 6×10^{-6} and standard deviation σ, and the test statistic $T = \hat{\delta}/\sigma$, with mean $\delta/\sigma = .000217 \times N^{1/2}$ and unit standard deviation.

Under these assumptions the power of the test, as a function of sample size, is approximately

$$\text{Power}\ (N) = \Phi\ (\delta/\sigma - 1.645)$$

where Φ is the standard normal probability function. Power, graphed in the left-hand panel of Fig. 1, reaches the 50 percent level only when the sample size is about 60 million. For a sample of 10 million power is only 17 percent, and the probability of a negative estimate, $\Phi(-\delta/\sigma)$, is 25 percent. At $N = 1$ million, power is only a little above the minimum value of 5 percent and the probability of a negative estimate is nearly 50 percent, while with N above 100 million, where power climbs above 70 percent, a negative estimate is very unlikely.

The minimum value of $\hat{\delta}$ leading to rejection, $1.645\sigma = .04550/N^{1/2}$, or $45{,}500/N^{1/2}$ excess cases per million per year, is graphed in the right-hand panel of Fig. 1. The curve above it is the average of all values of $\hat{\delta}$ leading to rejection, given by

$$\delta + \sigma\ \phi(\delta/\sigma - 1.645)/\Phi(\delta/\sigma - 1.645)$$

where ϕ denotes the standard normal density function, the first derivative of Φ. Only when power is above 50 percent (at N about 60 million) is the minimum statistically significant estimate less than the assumed true excess, and only for N greater than about 100 million does the bias imposed by a policy of noticing only significant estimates drop below 25 percent. For a sample size of 10 million the upward bias is 218 percent (the minimum significant estimate is 139 percent too high), and at 1 million the bias is 866 percent (minimum 658 percent).

Case-Control Samples

Obviously a sample of 100 million women would be impracticable. On the other hand, the case-control approach, in which the sample consists of a fixed number of breast cancer cases and a fixed number of matched noncases, or controls, and in which cases and controls are compared with respect to frequency of exposure, also would require an impracticably large sample size. For example, if four controls were selected for each case and if about half of all women were exposed, about 600,000 breast cancer cases would be needed for power comparable to that from a cohort study of 100 million women (*15*). In the United States each year there are about 25,000 new cases of breast cancer among wom-

en between the ages of 45 and 54 (*13*) or about 1/24 the number required.

For studying larger average breast-tissue doses, assuming excess risk to be proportional to dose, disproportionately fewer women would be required. With the cohort approach, 1 million women would be required if the average dose were 10 rad instead of 1 rad, and only 11,000 would be required if it were 100 rad. Similarly smaller sample sizes would serve for the case-control approach.

Example: Leukemia

The very large sample size requirement of the above example is a consequence of the small expected radiation effect relative to the underlying breast cancer rate in the population. A smaller sample would be required for study of a cancer with a similar radiation effect but a lower population rate. For example, if instead of breast cancer in women exposed to a 1-rad breast-tissue dose, we consider leukemia in men of the same age with a 1-rad bone-marrow dose, followed for 15 years after exposure, the normal leukemia incidence of 44 cases per million per year might be increased by as much as three cases per million per year in the exposed group (*16*). The sample size required for this example is about 1/15 that for the breast cancer example, but it is nonetheless very large. A case-control study with approximately the same statistical properties as a cohort study of 16 million men would require about 1300 cases, assuming a 50 percent exposure rate and four controls per case (*15*). The number of cases required is a little over twice the annual number of new leukemia cases among U.S. men in the age range 35 to 49 (*13*).

Confidence Intervals

Many of the inference problems associated with studies of low power, as discussed above, are behavioral in nature and involve misuses of statistics. That is, if we report, or pay attention to, only those point estimates of excess risk that are significantly greater than zero, we introduce bias that can be considerable when power is low but that tends to be relatively unimportant when power is high. Similarly, the bias introduced by ascribing undue importance to negative estimates is serious when power is low but not when power is high. These misuses of statistics have in common that point estimates of risk are evaluated with little or no regard to their precision. Because point estimates are imprecise when power is low, ignoring evidence about precision makes it easier to select data that appear to support a given point of view.

A confidence interval is a range of values—here, risk values—that are consistent with the data. In contrast to inferences based solely on point estimates and the result of a single hypothesis test, inferences based on confidence intervals emphasize statistical uncertainty and are therefore less subject to biases like those discussed above. This can be illustrated in terms of the example used to construct Fig. 1.

Given $N = 10$ million women, there is a 17 percent chance that a statistically significant point estimate of risk will be obtained, and such an estimate can be expected to be 3.2 times as large as the true risk. The probability that the true value will be excluded from the 95 percent right-infinite confidence interval is only 5 percent, however, and the chances of excluding all values less than twice the true value is only 1 percent. These probabilities correspond to conditional probabilities, given statistical significance, of .29 and .06, respectively. The probability of obtaining a negative point estimate of risk is 25 percent, but the chance that all positive risk values will be excluded from a one-sided, left-infinite confidence interval of level .95 is only 1 percent; the conditional probability of this, given a negative point estimate, is only 4 percent. Thus the confidence interval approach discourages extreme interpretations of study results by reminding us that less extreme interpretations also are consistent with the data.

Curve Fitting

With rare exceptions, estimates of cancer risk from low-dose radiation exposures must be based on information obtained by observing populations exposed to much higher doses. The simplest way to do this is to scale down the estimated excess risk at a higher dose level, for example by assuming the excess risk at 1 rad to be 1 percent of that estimated at 100 rad. Theoretical considerations, on the other hand, and much experimental and epidemiologic data, suggest a more complicated relation between dose and cancer incidence. A model widely accepted as consistent with existing knowledge represents carcinogenesis by an upward-curving "linear-quadratic" function of dose having positive slope and curvature at zero dose, and the competing effect of "cell killing," a general term used here to represent a loss of ability of cell division by an exponential multiplier:

$$I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2)\exp(-\beta_1 D - \beta_2 D^2)$$

Here D represents dose in rad and $I(D)$ cancer incidence or cancer mortality. The parameters α_0, α_1, α_2, β_1, and β_2, all of which are assumed to be nonnegative, correspond to the following concepts: α_0, cancer incidence in the absence of radiation; α_1, excess cancer incidence per rad at low doses; α_2, additional carcinogenic effect of multiple, closely spaced ionizing events as compared to single ionizing events, by which high-dose exposures have more effect per rad than low-dose exposures; and β_2 and β_1, analogs of α_1 and α_2, but for cell killing instead of carcinogenesis. Visually, $I(D)$ is an S-shaped curve which if it has

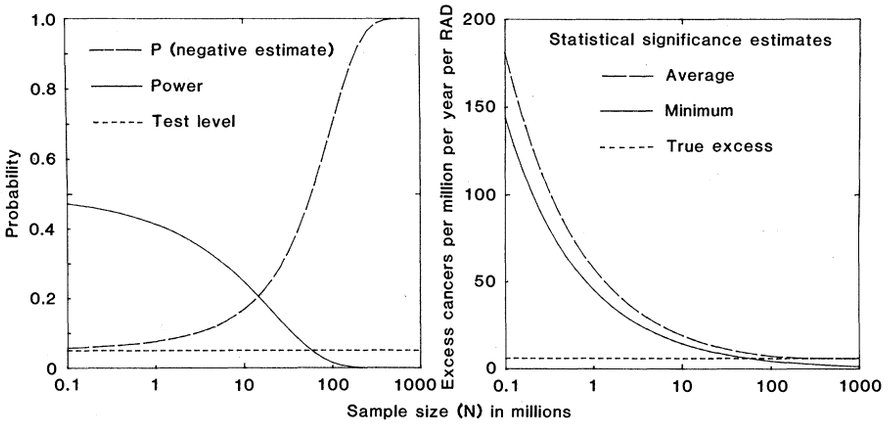

Fig. 1. Example: Hypothetical 20-year follow-up study of breast cancer incidence among N women, half of them exposed and half not exposed at age 35 to a breast-tissue dose of 1 rad. Assumed excess risk among the exposed is six breast cancers per million women per year after a 10-year minimum latency period. Statistical power, the probability of a negative risk estimate, and the minimum and average risk estimates given statistical significance at level .05 are plotted as functions of sample size N.

Table 1. Leukemia incidence among survivors of the Nagasaki atomic bomb and nonexposed controls, 1950 to 1971. [Data from Life Span Study sample (*7, 9*)].

Average dose to bone marrow (rads)	Person-years (PY) observation for risk	Leukemia rate per 10^4PY*	Estimated excess risk per 10^4 PY ± S.D.†
0	214,122‡	0.27	
2.1	128,288	0.48	0.21 ± 0.22
11.8	71,676	0.44	0.17 ± 0.27
38.9	25,643	0	−0.27 ± 0.71
79.0	27,355	1.86	1.59 ± 0.83
132	14,714‡	5.74	5.47 ± 1.98
186	5,415‡	3.51	3.24 ± 2.55
286	6,981	9.37	9.10 ± 3.67

*Adjusted to the age distribution of the entire LSS sample. †Standard deviation of rate minus zero-dose rate, assuming Poisson variation. ‡Numbers approximate, obtained by interpolation on year (*16*).

positive curvature anywhere has it at low dose levels and if it has negative curvature anywhere has it at high dose levels. α_0 is the zero-dose intercept of the dose-response curve, α_1 its slope at zero dose, and α_2 a constant multiple of the curvature near zero, while β_1 and β_2 correspond to the downward curvature at high dose levels (*1-3*).

Unfortunately, the dose-response curves observed for different cancers and species vary to such an extent that none of the parameters can be assumed known, nor can any two of these parameters be assumed to have a fixed relation to each other. The general model given above, with its five free parameters, is consistent with a large family of possible dose-response curves. Two such curves, for example, may agree closely at, say, 200 rad but disagree markedly on the amount of excess risk at doses under 10 rad. Thus the influence of high-dose observations on estimates of excess risk from low-dose exposures is limited. Simpler models, with fewer free parameters, correspond to much more restricted families of curves and impose more structure on the relation between excess risk at high doses and that at low doses. High-dose data, therefore, have more to do with estimates of low-dose risk than when a more general model is assumed. Only when low-dose data are extremely strong (and we have seen in the previous section that the required sample sizes may be very large indeed) is it possible to use models of great generality when the ultimate purpose is estimation of risk at low doses. Simpler models can be obtained by eliminating one or more of the parameters, or by other assumptions that reduce the number of free parameters.

Such assumptions, of course, are not without consequences. If the parameters α_2, β_1, and β_2 are set equal to zero, so that a purely linear dose-response model is fitted, the parameter α_1 retains its former meaning only if the linear model is assumed to be true. If, on the other hand, the linear model is used only as a first-order approximation to a dose response that is acknowledged to be more complex, the parameter α_1 is not the excess risk per rad at low doses but the average risk per rad over the entire fitted dose range.

A-Bomb Survivors

The Life Span Study (LSS) sample of Hiroshima and Nagasaki A-bomb survivors (*6*) is the largest and most detailed source of human dose-response data on radiation-induced cancer. These data are unique in having a wide range of estimated radiation doses, with the greatest numbers at the low end of the dose scale and with individual dose estimates accurate to within ± 30 percent (*17*). While the sample size is not nearly large enough at low doses for direct estimation of α_1 from low-dose data, curve fitting of general functions is much more feasible with these data than with data from other sources.

In the two examples presented below, four models—linear, linear-quadratic, linear with cell killing, and linear-quadratic with cell killing—have been fitted to age-standardized dose-response data from the LSS sample. The functional forms of the models are shown later in a table. All these models are simplified

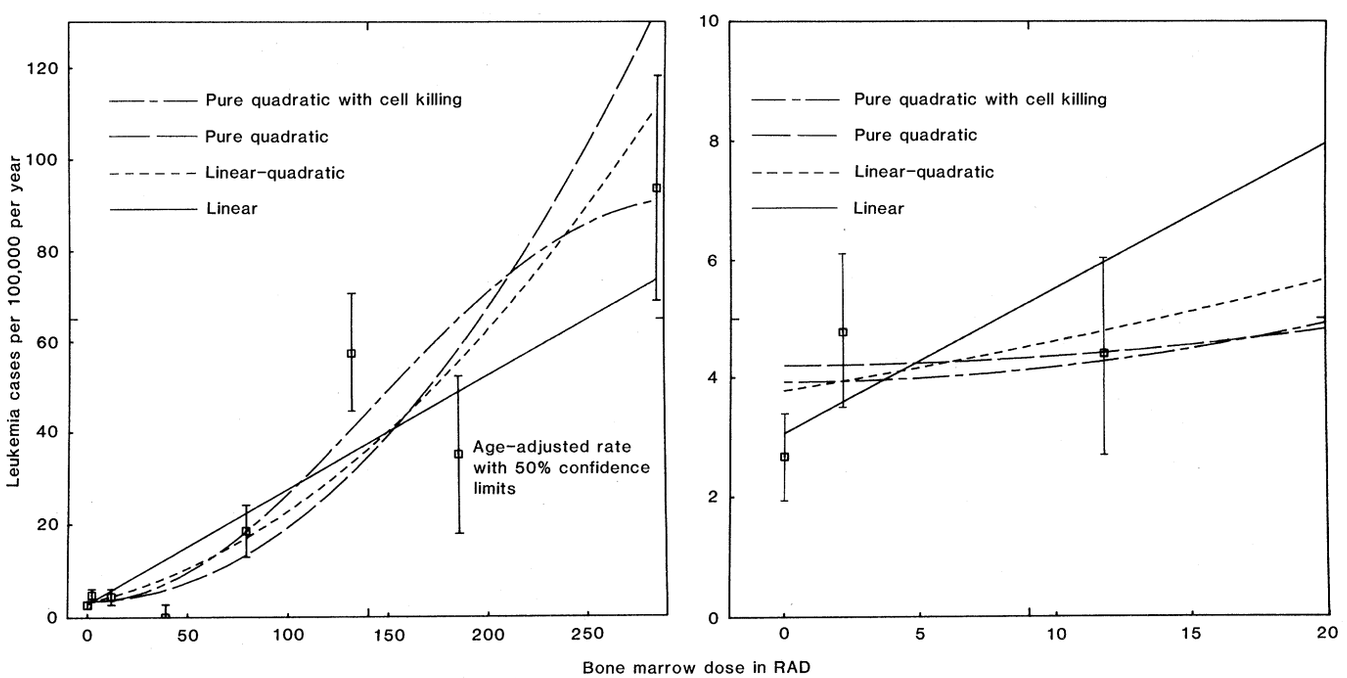

Fig. 2. Example: Dose-response analyses of leukemia incidence, 1950 to 1971, among Nagasaki A-bomb survivors. The right-hand panel is a detail of the left-hand panel. Age-adjusted rates are given with approximately 50 percent confidence limits. Fitted curves correspond to different dose-response models given in the text.

versions of the general model given previously. The linear model corresponds to a straight line; the linear-quadratic model to a curve with only upward curvature; the linear model with cell killing to a curve with only downward curvature, and that mainly at high dose; and the linear-quadratic model with cell killing to an S-shaped curve similar to that of the general model. (For the examples presented here, the linear-quadratic model with cell killing is very little different from the general model; either of the parameters β_1 and β_2 could be set equal to zero, and it was decided more or less arbitrarily to dispense with β_1.)

These simplified models all include a linear term, denoted by $\alpha_1 D$, which expresses most of the excess risk at low dose levels. It is more difficult to justify the use of a model without this term, since by omitting it one effectively assumes that the low-dose effects of radiation are negligible. Nevertheless, such models are favored by more than a few workers in the field, notably Rossi and Kellerer (*18*), as being consistent with radiobiological principles and with some experimental and epidemiological data. Two such models, pure quadratic and pure quadratic with cell killing, will also be fitted to sample data sets.

Table 1 and Fig. 2 show age-adjusted leukemia incidence rates by average bone-marrow dose for Nagasaki A-bomb survivors of both sexes, during the period 1950 to 1971 (*19*). Rates are shown with approximate 50 percent confidence limits as determined separately from each dose-specific rate. Data from the Hiroshima survivors are not included because the two cities show very different dose-response relations for leukemia; this difference is usually attributed to the substantial neutron component of radiation dose from the Hiroshima bomb. In the analyses presented below no account is taken of latent period or variations in radiation sensitivity by age at exposure, other than to adjust for possible confounding with dose. Therefore, the estimates pertain only to a population of similar age distribution observed over a similar time period following exposure (5 to 26 years).

In this example, the estimates of the parameter β_2 in the linear model with cell killing and of the parameter α_1 in the linear-quadratic model with cell killing were zero, under the constraint that all parameter values be nonnegative. That is, the best-fitting curves under these two models coincided with the best-fitting curves under the linear model and the pure quadratic model with cell killing, respectively (Table 2). Each of the models fitted the data adequately, according to chi-square values for goodness of fit, and none gave a statistically significant improvement in fit over any other. The standard deviations of the parameter estimates declined with increasing complexity of the dose-response model. The influence of assumptions about the dose response can be seen vividly in the estimates of excess risk at 1 rad, which ranged from .026 to 2.5 excess cases per million per year for models having a linear term in dose and down to .016 for the pure quadratic model (Table 2 and right-hand panel of Fig. 2).

Table 3 shows age-adjusted breast cancer incidence rates by breast-tissue

Table 2. Summary of curve-fitting analyses of age-adjusted leukemia incidence data.

Model and equation	Parameter: estimate + S.D.*	Analysis for lack of fit		
		χ^2	d.f.†	P
Linear $I(D) = \alpha_0 + \alpha_1 D$	α_1 : 2.5 ± 0.6	6.9	6	.33
Linear-quadratic $I(D) = \alpha_0 + \alpha_1 D + \alpha_2 D$	α_1 : 1.0 ± 1.2 α_2 : .010 ± .008	6.3	5	.28
Linear with cell killing $I(D) = (\alpha_0 + \alpha_1 D) \exp(-\beta_2 D^2)$	α_1 : 2.5 ± 1.0 β_2 : 0 ± 8.4‡	6.9	5	.23
Linear-quadratic with cell killing $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) \exp(-\beta_2 D^2)$	α_1 : 0 ± 1.8‡ α_2 : .026 ± .028 β_2 : 11. ± 11.	4.7	4	.32
Pure quadratic $I(D) = \alpha_0 + \alpha_2 D^2$	α_2 : .016 ± .004	7.7	6	.26
Pure quadratic with cell killing $I(D) = (\alpha_0 + \alpha_2 D^2) \exp(-\beta_2 D^2)$	α_2 : .026 ± .010 β_2 : 11. ± 7.0	4.7	5	.45

*Estimate and standard deviation scaled by 10^6. †Degrees of freedom. ‡Boundary value estimate. Parameters constrained to be nonnegative. Standard deviation is approximately that of the negative estimate obtained by fitting the corresponding unconstrained model.

Table 3. Breast cancer incidence among female survivors of the Nagasaki atomic bomb, and nonexposed controls, 1950 to 1974.[Data from Life Span Study sample (*20*, *27*)]

Average dose to breast tissue (rads)	Person-years (PY) observation for risk	Breast cancer rate per 10^4 PY*	Estimated excess risk per 10^4 PY ± S.D.†
0	149,365	1.70	
1.9	40,933	1.87	0.17 ± 0.76
5.6	38,769	1.75	0.05 ± 0.75
13.0	26,578	1.65	−0.05 ± 0.86
33.6	18,288	3.10	1.40 ± 1.34
70.8	15,962	2.09	0.39 ± 1.19
143.0	17,883	5.43	3.73 ± 1.77
240.5	5,844	10.68	8.98 ± 4.29
343.7	2,456	4.53	2.83 ± 4.31
585.6	2,394	11.13	9.43 ± 6.83

*Adjusted to the age distribution of the entire LSS sample. †Standard deviation of rate minus zero dose rate, assuming Poisson variation.

Table 4. Summary of curve-fitting analyses of age-adjusted breast cancer incidence data.

Model and equation	Parameter: estimate ± S.D.*	Analysis for lack of fit		
		χ^2	d.f.†	P
Linear $I(D) = \alpha_0 + \alpha_1 D$	α_1 : 2.2 ± 0.4	3.3	8	.91
Linear-quadratic $I(D) = \alpha_0 + \alpha_1 D + \alpha_2 D^2$	α_1 : 2.2 ± 0.8 α_2 : 0 ± .0024‡	3.3	7	.86
Linear with cell killing $I(D) = (\alpha_0 + \alpha_1 D) \exp(-\beta_2 D^2)$	α_1 : 2.6 ± 0.6 β_2 : 1.2 ± 1.4	2.8	7	.90
Linear-quadratic with cell killing $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) \exp(-\beta_2 D^2)$	α_1 : 1.5 ± 1.5 α_2 : 0.0084 ± .0109 β_2 : 4.0 ± 2.8	2.6	6	.86
Pure quadratic $I(D) = \alpha_0 + \alpha_2 D^2$	α_2 : 0.0062 ± .0024	9.4	8	.31
Pure quadratic with cell killing $I(D) = (\alpha_0 + \alpha_2 D^2) \exp(-\beta_2 D^2)$	α_2 : 0.019 ± .005 β_2 : 5.7 ± 1.6	3.0	7	.89

*Estimate and standard deviation scale by 10^6. †Degrees of freedom. ‡Boundary value estimate. Parameters constrained to be nonnegative. Standard deviation is approximately that of the negative estimate obtained by fitting the corresponding unconstrained model.

dose for female survivors in Nagasaki, 1950 to 1974 (*14, 20*). For all models except the pure quadratic the pattern was the same as with the leukemia data; all were in good agreement with the data, and there were no differences with respect to goodness of fit (Table 4). The pure quadratic model, however, could be improved upon by the addition of a linear term in dose, or by adding a term to allow for cell killing.

The leukemia and breast cancer data presented here are among the very best human dose-response data available linking cancer risk with exposure to sparsely ionizing radiation, such as gamma ray or x-ray. Although these data have been simplified by adjusting for differences with respect to age, only the simplest dose-response models yielded estimates for excess risk at low doses for which the standard deviation was less than half the value of the estimate, and there was enormous variation according to which simple model was assumed. In fact, there was far more variation between the linear and the pure quadratic model estimates for both breast cancer and leukemia than there was between estimates for the two kinds of cancers with either model; thus the choice of model can have more influence on the estimate of excess risk at low doses than the data themselves. Much of the current controversy about levels of risk from low-dose radiation stems from disagreements about which simple models should be used to obtain estimates.

Discussion

There seems to be no way to evade the problem of curve fitting and extrapolation from high-dose estimates of excess risk. We do not have the resources for adequate epidemiologic studies of populations exposed to low levels of radiation, and if we should try to do them anyway we would run considerable risk of obtaining misleading results, results that would derive at least some credibility from the vast effort of obtaining them.

Of course, no unexpectedly high risk estimates based on studies of populations exposed to low-dose radiation can be rejected out of hand. Each study must be evaluated on its own merits and in the light of other information. One such estimate, by Stewart *et al.* (*21*) of increased childhood cancer mortality following exposure in utero to x-ray pelvimetry, has received support from other studies, including one by MacMahon *et al.* (*22*) in which a number of possible biases that might have affected the earlier study were eliminated. A recent striking example of an unusually high risk estimate that did not hold up under examination was the finding by Najarian and Colton (*23*) of a marked tendency for cancer deaths among former workers at the Portsmouth Naval Shipyard in New Hampshire to be concentrated among former nuclear workers, whose exposures had been kept to fairly low levels. A reexamination of the data by Colton *et al.* (*24*), using employment records instead of information provided by next of kin, showed the earlier finding to have been heavily influenced by response bias, decedents having been much more likely to be identified as nuclear workers by their relatives if the cause of death was cancer than if it was something else.

It is to be hoped that experimental and theoretical work will narrow the range of possible dose-response functions in such a way that more efficient use can be made of existing and future data. In the meantime, simple dose-response models have their uses. An argument for the use of radiation gains credibility if benefit outweighs risk even according to a model which tends to give high risk estimates, such as the linear model with cell killing, and an argument against such use is helped if risk according to a model which tends to give lower estimates, such as the pure quadratic or even the linear-quadratic model, outweighs benefit. Also, the linear model may adequately represent the true dose-response relation over a restricted dose range, such as 0 to 100 rad. Thus large epidemiologic studies of populations exposed to between, say, 20 and 100 rad may represent a viable compromise betwen the direct approach and extrapolation from very high-dose levels.

Comparisons of human data from populations exposed to different kinds of radiation, or to radiation distributed differently over time, can also be highly informative. For example, much higher levels of excess leukemia risk have been observed among survivors of the Hiroshima bomb than among Nagasaki survivors with similar estimated dose levels (*18, 19, 25*). This suggests that neutrons may be more effective than gamma rays in causing leukemia and, according to widely accepted microdosimetric principles (*26*), implies that the leukemia dose-response curve for x-rays or gamma rays should have substantial upward curvature. According to this interpretation, linear model estimates obtained by curve fitting to data covering a wide range of gamma ray dose probably tend to overestimate excess risk at low doses. It does not necessarily follow that the pure quadratic model is correct; the above considerations merely suggest that the more general linear-quadratic model is preferable to the simple linear model. In fact, the existence of a densely ionizing part of all gamma ray tracks requires that the linear coefficient of dose should be nonzero (*2*).

A different situation obtains for breast cancer. Here the observed dose-response relations are similar for Hiroshima and Nagasaki survivors, suggesting approximate equivalence of effect for neutrons and gamma rays (*14, 20, 27*). The combined data from the two cities, without distinction between neutron and gamma ray components, are strongly linear, providing no statistical support for any of the more general models considered here (*14, 28*). It is interesting that the evidence in favor of linearity has become stronger with time, as more breast cancer cases have been observed in the LSS sample (231 in 1950 to 1969 against 360 in 1950 to 1974) (*14, 20, 27, 28*). Additional evidence in favor of linearity comes from a comparison of the A-bomb survivor data with data from two medically exposed populations, women given between 1 and 11 fairly high-dose x-ray treatments for acute postpartum mastitis (*29*) and female tuberculosis patients exposed to an average of 100 chest fluoroscopy examinations at biweekly intervals, with around 1.5 rad per examination, in conjunction with lung-collapse therapy (*30*). The breast cancer response to the highly fractionated fluoroscopy exposures might be expected to be linear in dose, on radiobiological grounds (*1*). That the average excess risk per rad should agree closely with that observed among the mastitis patients and the A-bomb survivors of comparable ages at exposure, in spite of the fact that the doses to the latter populations were delivered over relatively short periods of time, is difficult to reconcile with strongly nonlinear dose-response assumptions (*14*). This is an example of how largely high-dose data sometimes can be used not only to calculate low-dose risk estimates according to a simple dose-response model but also to justify that model as approximately correct.

There does not appear to be a single, simple dose-response model that applies to all forms of radiation-induced cancer. Except for special cases such as childhood cancer caused by fetal irradiation, for which the radiation effect appears particularly strong, it seems unlikely that it will be possible to solve the problem of estimating precisely the cancer risks from low-dose radiation without first solving the more complicated problem of

determining the dose-response relations for particular cancers induced by radiation, over wide dose ranges. Paradoxically, it appears that in most cases there is more to be learned about cancer risks associated with low doses of radiation by studying populations with high and intermediate levels of exposure than by studying populations exposed only to low-dose radiation, even when the latter populations are very large.

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Federal Funding in Materials Research

James G. Ling and Mary Ann Hand

The relative merit of granting federal research funds to institutions rather than individual investigators has been a subject of controversy for some time. The recently formed National Commission on Research has included alternative funding mechanisms as one of the issues to be studied. This article summarizes the findings of a Mitre Corporation study performed between 1976 and 1978 on the Materials Research Laboratory (MRL) Program for the National Science Foundation (NSF). The study compared technical publications and other products of 16 MRL's, which had been funded with institutional grants, against similar material from individually funded research projects at 15 other universities (non-MRL's). Two universities funded with institutional grants by the Department of Energy (DOE) for materials research and two funded by the National Aeronautics and Space Administration (NASA) were also included in the study. In addition, the study compared total administrative costs (government plus university) per grant dollar for institutionally funded projects and those funded individually.

The primary objective of the study was to compare the effectiveness of institutional funding for MRL's with that of project funding for materials research. Emphasis was placed on the principal results and impacts of the MRL program since its inception in 1961, with particular focus on the period after NSF assumed sponsorship in 1972. Five investigators were involved in the study full-time for about 18 months.

Background of the MRL Program

The MRL program had its origin in the Interdisciplinary Laboratory (IDL) Program established in 1960 by the Advanced Research Projects Agency (ARPA) of the Department of Defense. The ARPA action was taken in response to a concern within the government that major hardware research and development programs were being impeded by the failure of materials technology to keep pace with needs.

Forty-five universities submitted proposals to establish IDL's, and 12 were selected. The funding arrangements with these 12 universities were designed to encourage stability and long-term university commitments. One key feature allowed the universities to make capital investments for IDL buildings and to be paid back over a 10-year period by ARPA through "building use" charges. A second key feature was that initial contracts covered a 4-year period. At the end of each year, contracts were renewed for an additional year, maintaining 4-year forward funding. This "block" or institutional funding approach, allowed the laboratories thus established to allocate funds internally to research projects rather than requiring them to request funds from ARPA on a project-by-project basis.

In July 1972, the IDL program was transferred from ARPA to NSF and renamed the MRL program. The term "block funding" was also changed to "core funding," highlighting the fact that other NSF funds, in the form of project grants, were available to support individual research efforts at the institutions. By 1976, NSF had added four new MRL's, and its funding for the MRL program in fiscal year (FY) 1976 was $14.6 million.

Two other federal agencies, the Atomic Energy Commission (AEC) and NASA, also established IDL's in the 1960's. The two IDL's originally sponsored by the former are now sponsored by DOE, and NASA continues to sponsor two of the three that it originally established.

James G. Ling is director of the Program Implementation Division, Office of Energy Research, Department of Energy, Washington, D.C. 20585. Formerly he was group leader for program assessments in the Department of Energy Planning and Analysis at the Mitre Corporation. Mary Ann Hand is a member of the technical staff of the Mitre Corporation, McLean, Virginia 22102.

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